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| Complete Specification entitled | (54) | PHARMACEUTICAL COMPOSITIONS USEFUL IN THE TREATMENT OF INVOLUNTARY MOVEMENT DISORDERS |
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| Related Art | (56) | Nil |

The following statement is a full description of this invention, including the best method of performing it known to us:

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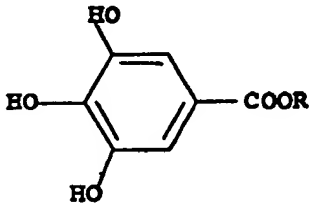
L230-40-ND-1 P. C.

The present invention pertains to pharmaceutical compositions useful in the treatment of involuntary disorders such as parkinsonism, Huntington's chorea, hyperkinesis, spasmotic torticollis and the like and especially to a method of potentiating the anti-Parkinson activity of L-DOPA.

More particularly the present invention relates to compositions containing 3-(3,4-dihydroxyphenyl)-L-alanine (L-DOPA) and a compound of the formula




wherein R is hydrogen or alkyl of from 1 to 9 carbon atoms or, when R is hydrogen, a pharmaceutically acceptable non-toxic alkali metal, alkaline earth metal or organic amine salt thereof, i.e. a salt of gallic acid.

The alkyl groups meant can be straight or branch-chained and include such groups as methyl, ethyl, propyl, isopropyl, butyl, pentyl, octyl, nonyl and the like.

It is a well established fact that the concentration of 3,4-dihydroxyphenethylamine (dopamine) in the striatum of the brain is markedly decreased in humans suffering from Parkinson's disease. Attempts have been made to increase the amount of dopamine present by administration. It has been found however that dopamine does not enter the brain and consequently direct administration of dopamine has not proved to be useful. Other experiments have shown that the precursor of dopamine, namely L-DOPA, does enter the brain where it is

converted by decarboxylase to dopamine, and L-DOPA is thus effective in the treatment of the disease. However, the use of L-DOPA is limited by the very high dosages required to show any effect. Such dosages may go as high as 8g per day and can cause side effects such as nausea, anorexia and postural hypotension. By the sixth month of treatment over three-fourths of the patients developed some type of choreiform movements. This iatrogenic hyperkinesia appears to be the major side effect which limits the dose employed.

The present invention is based on the fact that gallic acids, its salts and its esters increase the concentration and prolong the duration of dopamine in the brain following the administration of L-DOPA, by inhibiting its metabolism via catechol-O-methyl transferase.

Thus gallic acid, its salts and its esters effectively enhance the pharmacological activity of L-DOPA, and make it possible to reduce the amount of L-DOPA necessary for treating Parkinson's disease without impairing the therapeutic effectiveness thereof. Consequently, therapeutic compositions containing a combination of L-DOPA and gallic acid, its salts and its esters are valuable in effecting an increase in dopamine in the brain in warm-blooded animals, especially mammals. These combinations are therapeutically valuable in treating Parkinson's disease. For instance, they reduce akinesia, rigidity and tremors, thus diminishing or eliminating symptoms such as difficulty of initiating movements, masklike face and propulsive gait.

The therapeutic compositions of the present invention demonstrate the property of increasing the dopamine content in the brain in warm-blooded animals when administered

orally or parenterally. They are thus useful in treating Parkinson's disease and its obvious symptoms such as akinesia, tremor, rigidity etc.

The therapeutic property of the compositions of the present invention can be conveniently observed in the laboratory model in which guinea pigs are used as test animals. In this test, reserpine is used to deplete brain catecholamines. The proper duration and dose of reserpine is ascertained before the test to ensure that in the test animals the dopamine level is depleted but newly synthesized dopamine is not destroyed. In this test, an i.p. injection of a composition containing 10 mg/kg of L-DOPA and 200 mg/kg of butyl gallate restores the dopamine content to control values in two hours. Gallic acid, its salts and its esters in conjunction with L-DOPA therapy can be observed in laboratory models, as well as in man. For example, on a monkey having mesencephalic lesions, doses of L-DOPA up to 25 mg/kg produced no change in the tremor. At half this dose of L-DOPA however, 12.5 mg/kg, when administered with either 10 or 15 mg/kg of butyl gallate, the tremor diminished for 40 minutes. When 12.5 mg/kg of L-DOPA was administered with 20 mg/kg of butyl gallate, the tremor ceased for from 40 to 60 minutes. In a second monkey, while 15 mg/kg of L-DOPA had no effect, 25 mg/kg of L-DOPA effected a cessation of tremor for 30 minutes and a diminished tremor for 45 minutes. However when 15 mg/kg of butyl gallate were administered, substantially the same effect was obtained with only 15 mg/kg of L-DOPA as observed for 25 mg/kg of L-DOPA alone, namely a diminished tremor for 40 minutes and a cessation of tremor for 20 to 30 minutes.

The combination of L-DOPA with gallic acid, its salt or an ester administered parenterally or orally in any of the usual pharmacuetical forms. These include solid and liquid unit oral dosage forms such as tablets, capsules, powders, suspensions, solutions, syrups and the like, including sustained release preparations, and fluid injectable forms such as sterile solutions and suspensions. The term dosage form as used in this specification and the claims refers to physically discrete units to be administered in single or multiple dosage to animals, each unit containing a predetermined quentity of active materials in association with the required diluent, carrier or vehicle. The quantity of active material is that calculated to produce the desired therapeutic effect upon administration of one or more of such units.

Powders are prepared by comminuting the composition to a suitably fine size and mixing with a similarly comminuted diluent pharmaceutical carrier such as an edible carbohydrate material as for example, starch. Sweetening, flavoring, preservative, dispersing and coloring agents can also be present.

Capsules are made by preparing a powder mixture as described above and filling formed gelatin sheaths. A lubricant such as talc, magnesium stearate and calcium stearate can be added to the powder mixture as an adjuvant before the filling operation; a glidant such as colloidal silica may be added to improve flow properties; a disintegrating or solubilizing agent may be added to improve the availability of the medicament when the capsule is ingested.

Tablets are made by preparing a powder mixture,

granulating or slugging, adding a lubricant and disintegrant and pressing into tablets. A powder mixture is prepared by mixing the composition, suitably comminuted, with a diluent or base such as starch, sucrose, kaolin, dicalcium phosphate and the like. The powder mixture can be granulated by wetting with a binder such as syrup, starch paste, acacia mucilage or solutions of cellulosic or polymeric materials and forcing through a screen. As an alternative to granulating, the powder mixture can be run through the tablet machine and the resulting imperfectly formed slugs broken into granules. The granules can be lubricated to prevent sticking to the tablet forming dies by means of the addition of stearic acid, a stearate salt, talc or mineral oil. The lubricated mixture is then compressed into tablets, the medicaments can also be combined with free flowing inert carriers and compressed into tablets directly without going through the granulating or slugging steps. A protective coating consisting of a sealing coat of shellac, a coating of sugar or polymeric material and a polish coating of wax can be provided. Dyestuffs can be added to these coatings to distinguish different unit dosages.

Oral fluids such as syrups and elixirs can be prepared in unit dosage form so that a given quantity, e.g., a teaspoonful, contains a predetermined amount of the composition. Syrups can be prepared by dissolving the composition in a suitably flavored aqueous sucrose solution while elixirs are prepared through the use of a non-toxic alcoholic vehicle. Suspensions can be formulated by dispersing the medicament in a non-toxic vehicle in which it is insoluble.

For parenteral administration, fluid unit dosage

forms can be prepared by suspending or dissolving a measured amount of the composition in a non-toxic liquid vehicle suitable for injection such as an aqueous or oleaginous medium. Alternatively a measured amount of the composition is placed in a vial and the vial and its contents are sterilized and sealed. An accompanying vial or vehicle can be provided for mixing prior to administration.

The amount of therapeutic composition which is administered in use to effect an increase in dopamine in the brain must in all cases be adjusted to the animal being treated, its age, weight and condition as well as the degree of response required. Thus, while an anti-Parkinson response is observed for these compositions containing from about 5 mg/kg to about 50 mg/kg of L-DOPA and about 50 mg/kg to about 1000 mg/kg of an alkyl gallate, gallic acid or its salt, the actual dose should be carefully titrated to the particular subject in accordance with well recognized principles of pharmacology. A particularly favorable composition contains besides L-DOPA from about 1 to 20 times the the amount of gallic acid its salt or an ester thereof, preferably from about 5 to 20 times the amount.

The method of potentiating the anti-Parkinson property of L-DOPA comprises the internal administration of L-DOPA in combination with 1 to 20 times the amount of gallic acid its salt or an ester thereof in dosage unit forms. The term unit dosage form referring to physically discrete units suitable as unitary dosages for warm blooded animals, each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect in association with the required pharmaceutical diluent, carrier

or vehicle.

The synthesis of gallic acid esters have been described in the literature by several authors: e.g. by W. Will, Ber. 21, 2022 (1888); H. Meyer, Monatsheffe 19, 594; Dutch Patent 66,611; A. Russell and W. G. Tebbeus, J.A.C.S. 64, 2274-6 (1942); W. G. Christiansen, J.A.C.S. 48, 1361 (1926); all gallic acid esters claimed in the present invention can be prepared according to or in analogy to the processes therein described.

The following examples are given by way of illustrating the compositions without limiting the scope thereof in any way.

EXAMPLE 1

| Ingredient | Quantity/capsule |
|---|---|
| L-DOPA | 100 mg |
| Butyl gallate | 200 mg |
| Corn Starch | 500 mg |

The foregoing ingredients are mixed and introduced into a two-piece No. 1 hard gelatin capsule.

EXAMPLE 2

| Ingredient | Quantity/tablet |
|---|---|
| L-DOPA | 100 mg |
| Butyl gallate | 300 mg |
| Corn Starch U.S.P. | 150 mg |
| Lactose | 200 mg |
| Cab-O-Sil M 5 | 4 mg |
| Gelatin U.S.P. | 5 mg |
| Magnesium Stearate U.S.P. | 1 mg |

The L-DOPA, butyl gallate, corn starch and lactose are thoroughly blended and granulated with a 10% aqueous

solution of gelatin. The wet granulate is dried, screened and combined with the Cab-O-Sil and magnesium stearate. This mixture is pressed into tablets suitable for oral administration of 100 mg of L-DOPA and 300 mg of butyl gallate. The tablets may be scored to permit the administration of fractional doses.

EXAMPLE 3

| Ingredient | Quantity/tablet |
|---|---|
| L-DOPA | 50 mg |
| Propyl gallate | 300 mg |
| Corn Starch U.S.P. | 200 mg |
| Lactose | 200 mg |
| Cab-O-Sil M 5 | 4 mg |
| Gelatin U.S.P. | 5 mg |
| Magnesium Stearate U.S.P. | 1 mg |

The foregoing ingredients are thoroughly mixed and pressed into tablets suitable for oral administration of 50 mg of L-DOPA active ingredient and 300 mg of propyl gallate active ingredient. The tablets may be scored to permit administration of fractional doses.

EXAMPLE 4

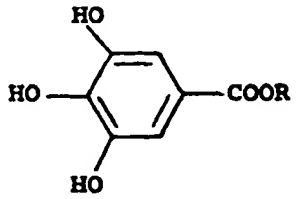
| Ingredient | Quantity/tablet |
|---|---|
| L-DOPA | 100 mg |
| Pentyl gallate | 250 mg |
| Lactose | 100 mg |
| Corn Starch | 100 mg |
| Soluble Starch | 15 mg |
| Magnesium Stearate | 5 mg |

The first four ingredients are thoroughly mixed and granulated with a solution of the soluble starch. This

granulate is dried, mixed with the magnesium stearate and pressed into tablet cores which are coated as with sugar.

The claims defining the invention are as follows:

1. Pharmaceutical composition comprising 3-(3,4-dihydroxyphenyl)-L-alanine and an alkyl gallate or gallic acid of formula




wherein R is hydrogen or an alkyl moiety of 1 to 9 carbon atoms, or, when R is hydrogen, a pharmaceutically acceptable non-toxic salt thereof, in combination with a pharmaceutically acceptable diluent or carrier therefor.

2. Pharmaceutical composition as claimed in claim 1 wherein from 1 to 20 parts per weight of an alkyl gallate or of gallic acid or its salt are present per part by weight of 3-(3,4-dihydroxyphenyl)-L-alanine.

3. Pharmaceutical composition as claimed in claim 1 wherein from 5 to 20 parts per weight of an alkyl gallate or of gallic acid or its salt are present per part of weight of 3-(3,4-dihydroxyphenyl)-L-alanine.

4. Pharmaceutical composition as claimed in claim 1, 2 or 3 wherein the alkyl gallate is butyl gallate.

5. Pharmaceutical composition as claimed in any one of the preceeding claims compounded in dosage unit form suitable for internal administration.

6. Pharmaceutical composition in unit dosage form suitable for internal administration and containing 3-(3,4-dihydroxyphenyl)-L-alanine and gallic acid, its salts or an alkyl gallate having maximally 9 carbon atoms in the alkyl

moiety.

7. Pharmaceutical composition as claimed in claim 6 wherein from 1 to 20 parts per weight of gallic acid, its salt or an alkyl gallate are present per part by weight of 3-(3,4-dihydroxyphenyl)-L-alanine.

8. Pharmaceutical composition as claimed in claim 6 wherein from 5 to 20 parts per weight of gallic acid, its salt or an alkyl gallate are present per part by weight of 3-(3,4-dihydroxyphenyl)-L-alanine.

9. A pharmaceutical composition substantially as herein described with reference to either of the foregoing Examples.

10. Method of treating Parkinson's disease which comprises administering 3-(3,4-dihydroxyphenyl)-L-alanine in combination with gallic acid, its salt or an alkyl gallate having at most 9 carbon atoms in the alkyl moiety.

11. Method as claimed in claim 10 wherein from 1 to 20 parts by weight of gallic acid, its salt or of the alkyl gallate are administered per part by weight of 3-(3,4-dihydroxyphenyl)-L-alanine.

12. Method as claimed in claim 10 wherein from 5 to 20 parts by weight of gallic, its salt or of the alkyl gallate are administered per part by weight of 3-(3,4-dihydroxyphenyl)-L-alanine.

13. Method as claimed in claims 10, 11 or 12 wherein the alkyl gallate is butyl gallate.

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